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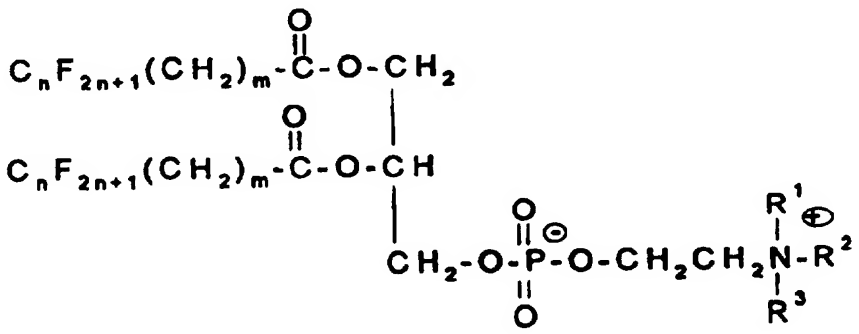

(I)

(57) Abstract

A pharmaceutical aerosol formulation which comprises particulate medicament, a fluorocarbon of hydrogen-containing chlorofluorocarbon propellant and a surfactant of general formula (I), wherein n is an integer of 1 to 18; m is an integer of 0 to 17; and R^1, R^2 and R^3 are each independently a hydrogen atom or a C_{1-4}alkyl group.

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MEDICAMENTS

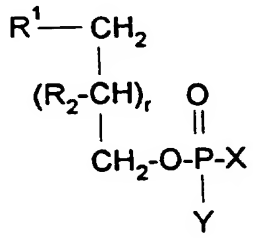
This invention relates to aerosol formulations of use for the administration of medicaments by inhalation.

The use of aerosols to administer medicaments has been known for several decades. Such aerosols generally comprise the medicament, one or more chlorofluorocarbon propellants and either a surfactant or a solvent, such as ethanol. The most commonly used aerosol propellants for medicaments have been propellant 11 (CCl_3F) and/or propellant 114 (CF_2ClCF_2Cl) with propellant 12 (CCl_2F_2). However these propellants are now believed to provoke the degradation of stratospheric ozone and there is thus a need to provide aerosol formulations for medicaments which employ so called "ozone-friendly" propellants.

A class of propellants which are believed to have minimal ozone-depleting effects in comparison to conventional chlorofluorocarbons comprise fluorocarbons and hydrogen-containing chlorofluorocarbons, and a number of medicinal aerosol formulations using such propellant systems are disclosed in, for example, EP 0372777, WO91/04011, WO91/11173, WO91/11495 and WO91/14422. These applications are all concerned with the preparation of pressurised aerosols for the administration of medicaments and seek to overcome the problems associated with the use of the new class of propellants, in particular the problems of stability associated with the pharmaceutical formulations prepared. The applications all propose the addition of one or more of adjuvants such as alcohols, alkanes, dimethyl ether, surfactants (including fluorinated and non-fluorinated surfactants, carboxylic acids, polyethoxylates etc) and even conventional chlorofluorocarbon propellants in small amounts intended to minimise potential ozone damage.

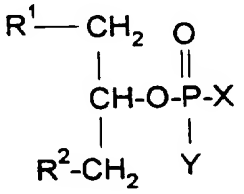
It is well established in the art that fluorinated surfactants may be used to stabilise micronised drug suspensions in hydrofluorocarbon propellants such as 1, 1, 1, 2-tetrafluoroethane (P134a), see for example US5126123, WO91/11173, WO91/14422 and WO92/00062. Surprisingly, the applicants have now found that a particular group of fluorinated surfactants may be used to prepare novel aerosol formulations, and can be advantageous in terms of reducing drug deposition, increasing shelf life and like.

Thus, in one aspect the invention provides a pharmaceutical aerosol formulation which comprises particulate medicament, a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant and a surfactant of general formula (Ia) or (Ib)



(Ia)

or



(Ib)

wherein:

R^1 represents:

$R_F(CH_2)_a$-$(CH=CH)_b$-$(CH_2)_c$-$(CH=CH)_d$-$(CH_2)_e$-A-;

R_F-$(CH_2)_f$-$OCH_2CH(CH_2OH)CH_2$-A-;

R_F-$(CH_2)_g$-$OCH_2CH(CH_2OH)$-A-;

wherein -A- represents -O-, -C(O)O-, $-R^6(R^7)N^+$-, (wherein each of R^6 and R^7 represents C_1-C_4 alkyl or hydroxyethyl), $-(CH_2)_t$-, wherein t=0 or 1 or $-C(O)N(R^9)-(CH_2)_q$-B, wherein q is an integer from 0 to 12, B represents -O- or -C(O)-, and R^9 is hydrogen or R^6,

and wherein the sum of a+c+e is from 0 to 17, especially 0 to 11, the sum b+d is from 0 to 12 and each of f and g is from 1 to 12;

R_F-$(CH_2$-CH_2-$O)_h$-;

R_F-$(CH(CH_3)CH_2O)_h$-;

R_F-$(-CH_2$-CH_2-$S)_h$-,

wherein h is from 1 to 12; and

wherein R_F represents a fluorine-containing moiety having one of the following structures:

(a) $F(CF_2)_i$-, wherein i is from 1 to 18, especially 2 to 12

(b) $(CF_3)_2CF(CF_2)_j$-, wherein j is from 0 to 8

(c) $R_F1(CF_2CF(CF_3))_k$-, wherein k is from 1 to 4, and R_F1 represents CF_3-, C_2F_5- or $(CF_3)_2CF$-,

(d) $R_F2(R_F3)CFO(CF_2CF_2)_l$ wherein l is from 1 to 6 and wherein each of R_F2 and R_F3 independently represents CF_3-, C_2F_5-, n-C_3F_7- or $CF_3CF_2CF(CF_3)$- or R_F2 and R_F3 taken together represent $-(CF_2)_4$- or $-(CF_2)_5$-, or

(e) one of the structures (a) to (d) in which one or more of the fluorine atoms are replaced by one or more hydrogen or bromine atoms and/or at least two

chlorine atoms in a proportion such that at least 50% of the atoms bonded to the carbon skeleton of R_F are fluorine atoms, and wherein R_F contains at least 4 fluorine atoms,

r is 0 or 1;

R^2 represents R^1, hydrogen or a group OR,

wherein R represents a saturated or unsaturated C_1-C_{20} alkyl or C_3-C_{20} acyl; and when r is 1, R^1 and R^2 may exchange their positions; and

each of X and Y independently represent:

hydroxyl;

$-OCH_2CH(OH)CH_2OH$;

$-O(CH_2CH_2O)_tR^3$,

wherein t is an integer from 1 to 5; and R^3 represents a hydrogen atom or C_1-C_4 alkyl group;

$-NR^4R^5$ or $N^+R^4R^5R^8$,

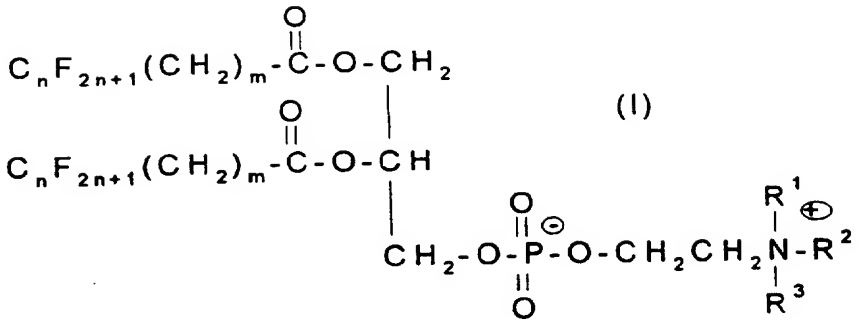
wherein each of R^4, R^5 and R^8 independently represents a hydrogen atom; a C_1-C_4 alkyl group, $-CH_2CH_2O(CH_2CH_2O)_sR^3$, wherein s represents an integer of from 1 to 5, or R^4 and R^5 when taken together represent $-(CH_2)_q$ wherein q is an integer of from 2 to 5, or with the nitrogen atom R^4 and R^5 form a morpholino group;

$-O(CH_2)_pZ$ wherein Z represents a 2-aminoacetic acid group, $-NR^4R^5$ or $-N^+R^4R^5R^8$ where R^8 is as defined for R^4 and R^5 above, and p is an integer of from 1 to 5;

with the proviso that X and Y do not both represent hydroxyl or an ionized form derived from hydroxyl.

The compounds of formula (Ia) and (Ib) are described in EP-0478686, which is incorporated herein by reference, and suitable compounds of formula (Ia) and (Ib) and processes for their preparation may readily be determined by reference thereto. However, the applicants have found that a particular group of compounds of formula (Ia) are especially preferred for use in the formulations of the present invention.

Thus, in a further aspect the invention provides a pharmaceutical aerosol formulation which comprises particulate medicament, a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant and a surfactant of general formula (I)



(I)

wherein n is an integer of 1 to 18, especially 2 to 12;
m is an integer of 0 to 17, especially 0 to 11; and
R^1, R^2 and R^3 are each independently a hydrogen atom or a C_{1-4}alkyl group.

Particularly preferred compounds of formula (I) are the fluorinated phosphatidylcholines wherein R^1, R^2 and R^3 each represent methyl, n is an integer of 4 to 8, especially 4 or 6, and m is an integer of 4 to 10, especially 4, 6 or 10.

Certain compounds of formula (I) may contain one or more chiral centres. It will be understood that compounds of formula (I) include all optical isomers of the compounds of formula (I) and mixtures thereof, including racemic mixtures thereof.

Contrary to the teaching in the art, the surfactants employed for the preparation of formulations according to the present invention are effective stabilisers at low concentrations relative to the amount of medicament. Thus, the amount of surfactant employed is desirably in the range of 0.005 to 20% w/w, particularly 0.05 to 20% w/w, more particularly 0.05 to 15% w/w, even more particularly about 0.1 to about 10% w/w, and preferably 0.5 to about 10% w/w, relative to the medicament.

The particle size of the particulate (e.g. micronised) medicament should be such as to permit inhalation of substantially all of the medicament into the lungs upon administration of the aerosol formulation and will thus be less than 100 microns, desirably less than 20 microns, and preferably in the range 1-10 microns, e.g. 1-5 microns.

The final aerosol formulation desirably contains 0.005-10% w/w, preferably 0.005 - 5% w/w, especially 0.01-1.0% w/w, of medicament relative to the total weight of the formulation.

Medicaments which may be administered in aerosol formulations according to the invention include any drug useful in inhalation therapy and which may be presented in a form which is substantially completely insoluble in the selected propellant. Appropriate medicaments may thus be selected from, for example, analgesics, e.g. codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g. diltiazem; antiallergics, e.g. cromoglycate, ketotifen or nedocromil; antiinfectives e.g. cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g. methapyrilene; anti-inflammatories, e.g. beclomethasone, flunisolide, budesonide, tipredane, triamcinolone acetonide or fluticasone; antitussives, e.g. noscapine; bronchodilators, e.g. ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, salbutamol, salmeterol, terbutaline, isoetharine, tulobuterol, orciprenaline, or (-)-4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl] amino]methyl]benzenemethanol; diuretics, e.g. amiloride; anticholinergics e.g. ipratropium, atropine or oxitropium; hormones, e.g. cortisone, hydrocortisone or prednisolone; xanthines e.g. aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, e.g. insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts (e.g. as alkali metal or amine salts or as acid addition salts) or as esters (e.g. lower alkyl esters) or as solvates (e.g. hydrates) to optimise the activity and/or stability of the medicament and/or to minimise the solubility of the medicament in the propellant.

Particularly preferred medicaments for administration using aerosol formulations in accordance with the invention include antiallergics, bronchodilators and antiinflammatory steroids of use in the treatment of respiratory disorders such as asthma by inhalation therapy, for example cromoglycate (e.g. as the sodium salt), salbutamol (e.g. as the free base or the sulphate salt), salmeterol (e.g. as the xinafoate salt), terbutaline (e.g. as the sulphate salt), reproterol (e.g. as the hydrochloride salt), a beclomethasone ester (e.g. the diproprionate), a fluticasone ester (e.g. the propionate) or (-)-4-amino-3,5-dichloro-α-[[[6-[2-(2-

pyridinyl)ethoxy]hexyl]amino]methyl]benzenemethanol. Salmeterol, especially salmeterol xinafoate, salbutamol, fluticasone propionate, beclomethasone dipropionate and physiologically acceptable salts and solvates thereof are especially preferred.

It will be appreciated by those skilled in the art that the aerosol formulations according to the invention may , if desired, contain a combination of two or more active ingredients. Aerosol compositions containing two active ingredients (in a conventional propellant system) are known, for example, for the treatment of respiratory disorders such as asthma. Accordingly the present invention further provides aerosol formulations in accordance with the invention which contain two or more particulate medicaments. Thus suitable combinations of bronchodilatory agents include ephedrine and theophylline, fenoterol and ipratropium, and isoetharine and phenylephrine aerosol formulations.

Preferred aerosol formulations in accordance with the invention comprise (a) an effective amount of a particulate bronchodilatory medicament, (b) an effective amount of a particulate antiinflammatory, preferably a steroidal antiinflammatory medicament, (c) a fluorocarbon or hydrogen - containing chlorofluorocarbon propellant, and (d) a surfactant of general formula (I). Particularly preferred aerosol formulations contain bronchodilators such as salbutamol (e.g. as the free base or as the sulphate salt), salmeterol (e.g. as the xinafoate salt) or isoprenaline in combination with an antiinflammatory steroid such as a beclomethasone ester (e.g. the diproprionate) or a fluticasone ester (e.g. the propionate). Alternatively aerosol formulations may contain a bronchodilator in combination with an antiallergic such as cromoglycate (e.g. the sodium salt). Combinations of isoprenaline and sodium cromoglycate, salmeterol and fluticasone propionate, or salbutamol and beclomethasone dipropionate are especially preferred.

The propellants for use in the invention may be any fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof having a sufficient vapour pressure to render them effective as propellants. Preferably the propellant will be a non-solvent for the medicament. Suitable propellants include, for example, C_{1-4}hydrogen-containing chlorofluorocarbons such as CH_2ClF, $CClF_2CHClF$, CF_3CHClF, CHF_2CClF_2, $CHClFCHF_2$, CF_3CH_2Cl and $CClF_2CH_3$; C_{1-4}hydrogen-containing fluorocarbons such as CHF_2CHF_2, CF_3CH_2F,

CHF_2CH_3 and CF_3CHFCF_3; and perfluorocarbons such as CF_3CF_3 and $CF_3CF_2CF_3$.

Where mixtures of the fluorocarbons or hydrogen-containing chlorofluorocarbons are employed they may be mixtures of the above identified compounds or mixtures, preferably binary mixtures, with other fluorocarbons or hydrogen-containing chloro- fluorocarbons for example $CHClF_2$, CH_2F_2 and CF_3CH_3. Preferably a single fluorocarbon or hydrogen-containing chlorofluorocarbon is employed as the propellant. Particularly preferred as propellants are C_{1-4}hydrogen-containing fluorocarbons such as 1,1,1,2-tetrafluoroethane(CF_3CH_2F) and 1,1,1,2,3,3,3-heptafluoro-n-propane (CF_3CHFCF_3).

It is desirable that the formulations of the invention contain no components which may provoke the degradation of stratospheric ozone. In particular it is desirable that the formulations are substantially free of chlorofluorocarbons such as CCl_3F, CCl_2F_2 and CF_3CCl_3.

The propellant may additionally contain a volatile adjuvant such as a saturated hydrocarbon for example propane, n-butane, isobutane, pentane and isopentane or a dialkyl ether for example dimethyl ether. In general, up to 50% w/w of the propellant may comprise a volatile hydrocarbon, for example 1 to 30% w/w. However, formulations which are substantially free of volatile adjuvants are preferred. In certain cases, it may be desirable to include appropriate amounts of water, which can be advantageous in modifying the dielectric properties of the propellant.

Polar cosolvents which may be incorporated into the formulations according to the present invention include (.e.g C_{2-6})aliphatic alcohols and polyols such as ethanol, isopropanol and propylene glycol and mixtures thereof. Preferably ethanol will be employed. In general only small quantities (e.g. 0.05 to 3.0% w/w) of polar cosolvent are required to improve the dispersion and the use of quantities in excess of 5% w/w may disadvantageously tend to dissolve the medicament. Formulations preferably contain less than 1% w/w, e.g. about 0.1% w/w of polar cosolvent. Polarity may be determined for example, by the method described in European Patent Application Publication No. 0327777.

In addition to the surfactants of general formula (I), the formulations according to the present invention may optionally contain one or more further ingredients conventionally used in the art of pharmaceutical aerosol formulation. Such optional ingredients include, but are not limited to, one or more conventional surfactants as hereinafter described and which are physiologically acceptable by inhalation, taste masking agents, one or more sugars, buffers, antioxidants, water and chemical stabilisers.

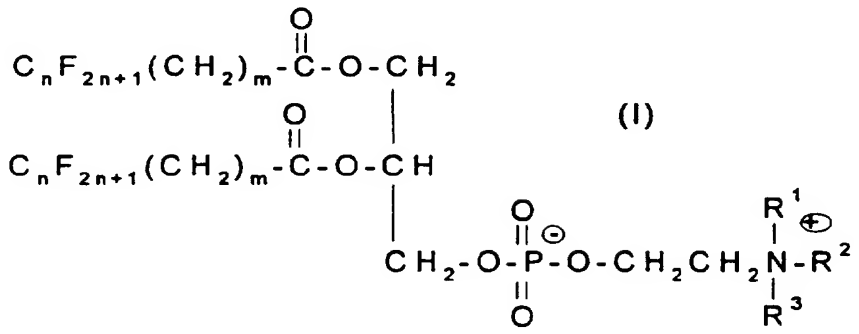
Examples of conventional physiologically acceptable surfactants include oleic acid, sorbitan trioleate (Span R 85), sorbitan mono-oleate, sorbitan monolaurate, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monooleate, natural lecithin, oleyl polyoxyethylene (2) ether, stearyl polyoxyethylene (2) ether, lauryl polyoxyethylene (4) ether, block copolymers of oxyethylene and oxypropylene, synthetic lecithin, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, isopropyl myristate, glyceryl monooleate, glyceryl monostearate, glyceryl monoricinoleate, cetyl alcohol, stearyl alcohol, polyethylene glycol 400, cetyl pyridinium chloride, benzalkonium chloride, olive oil, glyceryl monolaurate, corn oil, cotton seed oil and sunflower seed oil. Preferred surfactants are lecithin, oleic acid and sorbitan trioleate, for inclusion in a pharmaceutical formulation according to the present invention.

Aptly, the aerosol formulations according to the present invention may contain 0.0001 to 50% w/w, preferably 0.001 to 20, for example 0.001 to 1% of sugar relative to the total weight of the formulation. Generally the ratio of medicament : sugar falls within the range of 1:0.01 to 1:100 preferably 1:0.1 to 1:10. Typical sugars which may be used in the formulations include, for example, sucrose, lactose and dextrose, preferably lactose, and reducing sugars such as mannitol and sorbitol, and may be in micronised or milled form.

A particularly preferred embodiment of the invention provides a pharmaceutical aerosol formulation consisting essentially of one or more particulate medicament, one or more fluorocarbon or hydrogen-containing chlorofluorocarbon propellant and a surfactant of formula (I).

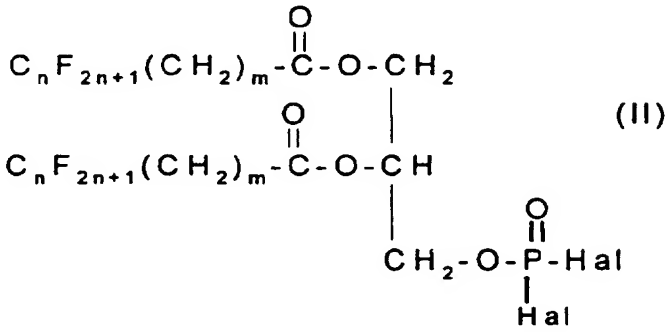
Surfactants according to the present invention can be prepared by techniques well known in the art, as can be seen for example, by reference to EP-0478686

substantially as hereinbefore described. A suitable process for preparing surfactants of compounds of formula (I)



(I)

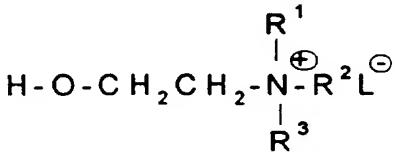
comprises reacting a compound of formula (II)



(II)

wherein Hal represents a halogen atom selected from fluorine, chlorine, bromine and iodine, with

(i) a compound of formula (III)



(III)

where L is a negatively charged counter ion, such as a halide or an alkyl or arylsulphonyloxy group, such as mesylate or tosylate, and

(ii) a hydroxylating agent, such as water.

Suitably the reaction may be carried out in the presence of a chlorinated organic solvent, such as chloroform or the like, and a basic medium, e.g. pyridine or the like.

Compounds of formulae (II) and (III) are well known in the art, and as described above, EP-0478686 is a suitable prior art document which can be referred to.

The formulations of the invention may be prepared by dispersal of the medicament and surfactant in the selected propellant in an appropriate container, e.g. with the aid of sonication. The process is desirably carried out under anhydrous conditions to obviate any adverse effects of moisture on suspension stability.

The chemical and physical stability and the pharmaceutical acceptability of the aerosol formulations according to the invention may be determined by techniques well known to those skilled in the art. Thus, for example, the chemical stability of the components may be determined by HPLC assay, for example, after prolonged storage of the product. Physical stability data may be gained from other conventional analytical techniques such as, for example, by leak testing, by valve delivery assay (average shot weights per actuation), by dose reproducibility assay (active ingredient per actuation) and spray distribution analysis.

The suspension stability of the aerosol formulations according to the invention is particularly impressive and may be measured by conventional techniques, for example by measuring flocculation size distribution using a back light scattering instrument or by measuring particle size distribution by cascade impaction or by the "twin impinger" analytical process. As used herein reference to the "twin impinger" assay means "Determination of the deposition of the emitted dose in pressurised inhalations using apparatus A" as defined in British Pharmacopaeia 1988, pages A204-207, Appendix XVII C. Such techniques enable the "respirable fraction" of the aerosol formulations to be calculated. As used herein reference to "respirable fraction" means the amount of active ingredient collected in the lower impingement chamber per actuation expressed as a percentage of the total amount of active ingredient delivered per actuation using the twin impinger method described above. The formulations according to the

invention have been found to have a respirable fraction of 20% or more by weight of the medicament, preferably 25 to 70%, for example 30 to 60%.

The formulations according to the invention may be filled into canisters suitable for delivering pharmaceutical aerosol formulations. Canisters generally comprise a container capable of withstanding the vapour pressure of the propellant used such as a plastic or plastic-coated glass bottle or preferably a metal can, for example an aluminium can which may optionally be anodised, lacquer-coated and/or plastic-coated, which container is closed with a metering valve. The metering valves are designed to deliver a metered amount of the formulation per actuation and incorporate a gasket to prevent leakage of propellant through the valve. The gasket may comprise any suitable elastomeric material such as for example low density polyethylene, chlorobutyl, black and white butadiene-acrylonitrile rubbers, butyl rubber and neoprene. Suitable valves are commercially available from manufacturers well known in the aerosol industry, for example, from Valois, France (e.g. DF10, DF30, DF60), Bespak plc, UK (e.g. BK300, BK357) and 3M-Neotechnic Ltd, UK (e.g. Spraymiser^{TM}).

Conventional bulk manufacturing methods and machinery well known to those skilled in the art of pharmaceutical aerosol manufacture may be employed for the preparation of large scale batches for the commercial production of filled canisters. Thus, for example, in one bulk manufacturing method a metering valve is crimped onto an aluminium can to form an empty canister. The particulate medicament is added to a charge vessel and liquified propellant is pressure filled through the charge vessel into a manufacturing vessel, together with liquified propellant containing the surfactant. The drug suspension is mixed before recirculation to a filling machine and an aliquot of the drug suspension is then filled through the metering valve into the canister. Typically, in batches prepared for pharmaceutical use, each filled canister is check-weighed, coded with a batch number and packed into a tray for storage before release testing.

Each filled canister is conveniently fitted into a suitable channelling device prior to use to form a metered dose inhaler for administration of the medicament into the lungs or nasal cavity of a patient. Suitable channelling devices comprise for example a valve actuator and a cylindrical or cone-like passage through which medicament may be delivered from the filled canister via the metering valve to

the nose or mouth of a patient e.g. a mouthpiece actuator. Metered dose inhalers are designed to deliver a fixed unit dosage of medicament per actuation or "puff", for example in the range of 10 to 5000 microgram medicament per puff.

Administration of medicament may be indicated for the treatment of mild, moderate or severe acute or chronic symptoms or for prophylactic treatment. It will be appreciated that the precise dose administered will depend on the age and condition of the patient, the particular particulate medicament used and the frequency of administration and will ultimately be at the discretion of the attendant physician. When combinations of medicaments are employed the dose of each component of the combination will in general be that employed for each component when used alone. Typically, administration may be one or more times, for example from 1 to 8 times per day, giving for example 1,2,3 or 4 puffs each time.

Suitable daily doses, may be, for example in the range 50 to 200 microgram of salmeterol, 100 to 1000 microgram of salbutamol, 50 to 2000 microgram of fluticasone propionate or 100 to 2000 microgram of beclomethasone dipropionate, depending on the severity of the disease.

Thus, for example, each valve actuation may deliver 25 microgram salmeterol, 100 microgram salbutamol, 25, 50, 125 or 250 microgram fluticasone propionate or 50, 100, 200 or 250 microgram beclomethasone dipropionate. Typically each filled canister for use in a metered dose inhaler contains 100, 160 or 240 metered doses or puffs of medicament.

The filled canisters and metered dose inhalers described herein comprise further aspects of the present invention.

A still further aspect of the present invention comprises a method of treating respiratory disorders such as, for example, asthma, which comprises administration by inhalation of an effective amount of a formulation as herein described.

The following non-limitative Examples serve to illustrate the invention.

Example 1

Example 1a

A compound of formula (I) (R^1, R^2, R^3=CH_3, n=6, m=6)

To a dry 1L four neck round bottom flask fitted with mechanical stirring, a temperature probe and nitrogen inlet, was added 150mL (5 volumes) of dry isopropyl ether (stabilised with BHT). The solution was cooled to -25°C and then 3.08mL (5.07g, 33.07mmol) of $POCl_3$ was added, followed by 5.53mL (4.02g, 39.68mmol) of triethylamine. The hazy solution was stirred for 5 minutes before the addition of 30.00g (31.50mmol) of 8,8,9,9,10,10,11,11,12,12,13,13,13-tridecafluoro-tridecanoic acid 3-hydroxy-2-(8,8,9,9,10,10,11,11,12,12,13,13,13-tridecafluorotridecanoyloxy)-propylester[1] in 75mL (2.5 vol) of isopropyl ether over a 20 minute time period, being sure to keep the internal temperature between -26 and -23°C. The mixture was allowed to warm up to 20°C over the course of 1 hour, and washed with 2 x 40mL (2.5 vol) of isopropyl ether, and then the filtrate was evaporated to a volume of about 100mL at 25°C. $CHCl_3$ (ethanol free 500mL) was added and the solution was evaporated at 25°C to a volume of about 100mL.

120mL (8.3 vol) of ethanol free chloroform was added. The solution was cooled to 0°C and then 12.8mL (12.3g, 155.6mmol) of pyridine and 9.56g (34.7mmol) of choline tosylate were added. The reaction mixture was allowed to warm up to 25°C over the course of 1 hour and then stirred for 7 hours at ambient temperature. Water 2.8mL (155.6mmol) was added and the mixture was stirred at 25°C for 5 hours. The mixture was stored overnight at 0°C, and then 250mL of absolute ethanol was added.

TMD-8 ion exchange resin (400g) was placed in a 600mL filter funnel. The resin was washed with absolute ethanol (3 x 250mL). The procedure yielded about 300g of resin after pulling a vacuum for an additional 15 minutes. The TMD-8 ion exchange resin (300g) was added and the suspension was stirred for 2 hours at 25°C. The resin was filtered, and the cake was washed with 3 x 250mL of absolute ethanol. The filtrate was stored overnight at 0°C, and then the solvent was evaporated at a temperature of 25 - 30°C to a total volume of 200mL. 500mL toluene was added, and the solvent was evaporated at 50°C to a volume of about 400mL at which time the product began to gel out of solution. 500mL toluene was added and the solvent was evaporated to a total volume of 500mL. The suspension was stirred vigorously for 12 hours at ambient

temperature and the solid powder was collected by filtration. The cake was washed with 2 x 200mL of toluene to afford 23.0g (65.4%) of the title compound.

Example 1b

A compound of formula (I) (R^1, R^2, R^3 = CH_3, n=4, m=10)

To a dry 2L four neck round bottom flask fitted with mechanical stirring, temperature probe, nitrogen inlet and septum, was added 100ml diethylether. The solution was cooled to -20°C, and then 6.7mL of $POCl_3$ was added, followed by 12.1mL of triethylamine. 62.5gm of 12,12,13,13,14,14,15,15,15-Nonafluoro-pentadecanoic acid 1-hydroxymethyl-2-(12,12,13,13,14,14,15,15,15-nonafluoro-pentadecanoyloxy)-ethyl ester[1] was dissolved in 500mL diethylether, chilled in an ice bath, and then added over a 30 minute time period to the $POCl_3$ solution. The mixture was allowed to warm to room temperature.

The mixture was filtered, and washed with 3 x 100mL diethylether, and the solvent removed under high vacuum. 100mL chloroform was added to dissolve the residue, followed by 200mL acetonitrile, 29.2mL pyridine and 10.1gm of choline chloride. The mixture was allowed to warm to room temperature, and then stirred under a nitrogen atmosphere overnight. 6.5mL of water was then added, and the reaction was stirred at room temperature over 2½hours.

The solvent was removed on rotary evaporation, and the resulting oil pumped under high vacuum for approximately 1 hour.

Meanwhile, 850g of ion exchange resin (TMD-8) was treated with 2 x 1L chloroform/methanol (4 : 1) mixture, 2 x 1L methanol and 1 x 1L chloroform/methanol (4 : 1).

The compound was diluted in 1,500mL chloroform, and the ion exchange resin was added, followed by stirring at room temperature for 2 hours. The solvent was then removed, the resultant filtrate rotary evaporated to an oil, and placed in the freezer overnight, and further purified to yield 27.58gm of the title compound.

Other surfactants of formula (I) described in the Examples hereinafter were prepared by analogous methods.

1. Prepared according to EP-0478686.

Example 2

Micronised salbutamol base (26mg) and compound of formula (I) (R^1,R^2,R^3 = CH_3, n=4, m=10) (5.1mg) were weighed into a 15ml transparent glass aerosol vial and a metering valve was crimped into place. 1, 1, 1, 2-Tetrafluoroethane (P134a,18.2g) and heptafluoropropane (P227, 21g) were added to the vial through the valve. The vial was sonicated for 30 sec. to disperse the drug and surfactant.

Examples 3-6

Using the procedure described in Example 2 the following formulations were prepared:

Example	Drug	Propellant	Surfactant/mg
3	Salbutamol base (26mg)	P227	1.2
4	Salbutamol base (26mg)	P227	11
5	Salbutamol sulphate (32mg)	P227	3.1
6	Salbutamol sulphate (32mg)	P134a	0.5

Examples 7 to 20

The aerosol formulations of Examples 7 to 20 were prepared in large scale batches. A metering valve (e.g. DF60 valve) was crimped into an 8ml aluminium can (12.5ml can in the case of Examples 19 and 20) and the can was purged with 1,1,1,2-tetrafluoroethane prior to filling. The particulate medicament (micronised) was added to a charge vessel and liquified 1,1,1, 2-tetrafluoroethane propellant was pressure filled through the charge vessel into a manufacturing vessel, together with liquified propellant containing the surfactant of formula (I) (R^1, R^2 and R^3 = CH_3, n and m as indicated). The drug suspension was mixed before recirculation to a filling machine and an aliquot (typically 12g) of the drug suspension was then filled through the metering valve into the canister to provide an inhaler typically containing an equivalent of 160 actuations of 75mg (designed to deliver 120 actuations). The following inhalers were prepared:

Example 7

	Per 75.0mg actuation	Per 160 actuations (i.e. per can)
Fluticasone propionate	275µg	44mg
Surfactant (n=4, m=4)	27.5µg	4.4mg
1, 1, 1, 2-Tetrafluoroethane	to 75.0mg	to 12.0g

Example 8

	Per 75.0mg actuation	Per 160 actuations (i.e. per can)
Fluticasone propionate	275µg	44mg
Surfactant (n=4, m=4)	2.75µg	0.44mg
1, 1, 1, 2-Tetrafluoroethane	to 75.0mg	to 12.0g

Example 9

	Per 75.0mg actuation	Per 160 actuations (i.e. per can)
Fluticasone propionate	275µg	44mg
Surfactant (n=6, m=6)	27.5µg	4.4mg
1, 1, 1, 2-Tetrafluoroethane	to 75.0mg	to 12.0g

Example 10

	Per 75.0mg actuation	Per 160 actuations (i.e. per can)
Fluticasone propionate	275µg	44mg
Surfactant (n=6, m=6)	2.75µg	0.44mg
1, 1, 1, 2-Tetrafluoroethane	to 75.0mg	to 12.0g

Example 11

	Per 75.0mg actuation	Per 160 actuations (i.e. per can)
Fluticasone propionate	27.5µg	4.4mg
Surfactant (n=4, m=4)	2.75µg	0.44mg
1, 1, 1, 2-Tetrafluoroethane	to 75.0mg	to 12.0g

Example 12

	Per 75.0mg actuation	Per 160 actuations (i.e. per can)
Fluticasone propionate	27.5µg	4.4mg
Surfactant (n=4, m=4)	0.275µg	0.044mg
1, 1, 1, 2-Tetrafluoroethane	to 75.0mg	to 12.0g

Example 13

	Per 75.0mg actuation	Per 160 actuations (i.e. per can)
Fluticasone propionate	27.5µg	4.4mg
Surfactant (n=6, m=6)	2.75µg	0.44mg
1, 1, 1, 2-Tetrafluoroethane	to 75.0mg	to 12.0g

Example 14

	Per 75.0mg actuation	Per 160 actuations (i.e. per can)
Fluticasone propionate	27.5µg	4.4mg
Surfactant (n=6, m=6)	0.275µg	0.044mg
1, 1, 1, 2-Tetrafluoroethane	to 75.0mg	to 12.0g

Example 15

	Per 75.0mg actuation	Per 160 actuations (i.e. per can)
Salmeterol xinafoate	39.88µg	6.38mg
Surfactant (n=4, m=4)	3.99µg	0.64mg
1, 1, 1, 2-Tetrafluoroethane	to 75.0mg	to 12.0g

Example 16

	Per 75.0mg actuation	Per 160 actuations (i.e. per can)
Salmeterol xinafoate	39.88µg	6.38mg
Surfactant (n=4, m=4)	0.399µg	0.064mg
1, 1, 1, 2-Tetrafluoroethane	to 75.0mg	to 12.0g

Example 17

	Per 75.0mg actuation	Per 160 actuations (i.e. per can)
Salmeterol xinafoate	39.88µg	6.38mg
Surfactant (n=6, m=6)	3.99µg	0.64mg
1, 1, 1, 2-Tetrafluoroethane	to 75.0mg	to 12.0g

Example 18

	Per 75.0mg actuation	Per 160 actuations (i.e. per can)
Salmeterol xinafoate	39.88µg	6.38mg
Surfactant (n=6, m=6)	0.399µg	0.064mg
1, 1, 1, 2-Tetrafluoroethane	to 75.0mg	to 12.0g

Example 19	Per 75.0mg actuation	Per 248 actuations (i.e. per can)
Beclomethasone dipropionate hydrate	54.32µg	13.47mg
Surfactant (n=6, m=6)	5.4µg	1.35mg
Purified water B.P.	0.045mg	11.16mg
1, 1, 1, 2-Tetrafluoroethane	to 75.0mg	to 18.6g

Inhaler contains equivalent of 248 actuations (delivers 200 actuations).

Example 20	Per 75.0mg actuation	Per 248 actuations (i.e. per can)
Beclomethasone dipropionate hydrate	54.32µg	13.47mg
Surfactant (n=4, m=4)	5.4µg	1.35mg
Purified water B.P.	0.045mg	11.16mg
1, 1, 1, 2-Tetrafluoroethane	to 75.0mg	to 18.6g

Inhaler contains equivalent of 248 actuations (delivers 200 actuations).

Examples 21 to 31

Micronized drug and surfactant were weighed into 15ml transparent aerosol vials (Wheaton Industries, NJ). A metering valve (Bespak valve No. BK300, or Valois DF60 MK VI) was crimped onto each vial. Finally, 1,1,1,2-tetrafluoroethane (P134a) or 1,1,1,2,3,3,3 - heptafluoro-n-propane (P227) was added to the vial through the valve. Vials were then sonicated for 30 seconds.

Example	Drug (amount)	Surfactant type	Surfactant mg/inhaler	Propellant P134a (18g) or P227 (22g)
21	Salbutamol Base (26mg)	n=8,m=4	2.0	P134a
22	Salbutamol Base (26mg)	n=6,m=10	1.8	P134a
23	Salbutamol Sulphate	n=6,m=10	2.3	P134a

	(29mg)			
24	Salbutamol Base (26mg)	n=4,m=10	1.2	P227
25	Salbutamol Base (26mg)	n=8,m=4	2.0	P227
26	Salbutamol Base (26mg)	n=6,m=10	2.8	P227
27	Salbutamol Sulphate (26mg)	n=8,m=4	2.0	P227
28	Salbutamol Sulphate (26mg)	n=6,m=10	2.0	P227
29	Salbutamol Sulphate (26mg)	n=4,m=10	3.1	P227
30	Salmeterol (9mg)	n=8,m=4	2.5	P227
31	Salmeterol (9mg)	n=6,m=10	3.0	P227

Examples 32 to 43

Stock solutions of surfactants with concentration of 0.33 mg/g were prepared in glass vials according to the following procedure. 6 mg of surfactant were weighed into the safety coated glass vials. A DF60 MKIV valve was crimped onto the vial using a Pamasol crimper. 18.2 grams of 1,1,1,2-tetrafluoroethane (P134a) were filled through the valve using a Pamasol pressure filler. Then, the inhalers were sonicated for 30 sec to disperse surfactants.

Appropriate amount surfactant or surfactant stock solution was delivered into the safety coated glass vials before a drug was added into these vials. A DF60 MKIV valve was crimped onto the canister, and P134a propellant as received was filled through the valve. After filling was complete, the inhalers were sonicated for 30 sec to disperse the drug and surfactant.

Example	Drug (amount)	Surfactant type	Surfactant mg/inhaler
32	Salbutamol Sulphate (29 mg)	n=4,m=10	1.0
33	Salbutamol Sulphate (29 mg)	n=4,m=4	1.0
34	Salbutamol Sulphate (29 mg)	n=6,m=6	1.0
35	Salbutamol Sulphate (29 mg)	n=8,m=4	1.0
36	Salmeterol (8 mg)	n=4,m=10	0.1
37	Salmeterol (8 mg)	n=4,m=4	0.1
38	Salmeterol (8 mg)	n=6,m=6	0.1

39	Salmeterol (8 mg)	n=8,m=4	0.1
40	Fluticasone Propionate(6mg)	n=4,m=10	1.0
41	Fluticasone Propionate(6mg)	n=4,m=4	1.0
42	Fluticasone Propionate(6mg)	n=6,m=6	1.0
43	Fluticasone Propionate(6mg)	n=8,m=4	1.0

Examples 44 to 51

Examples 44 to 51 were prepared as described for Examples 32 to 43 but using 1,1,1,2,-tetrafluoroethane (P134a) containing 600ppm of water. Wet propellant was made by mixing water and the propellant in a cylinder, and then shaking over night.

Example	Drug (amount)	Surfactant type	Surfactant mg/inhaler
44	BDP hydrate (12 mg)	n=4,m=10	1.0
45	BDP hydrate (12 mg)	n=4,m=4	1.0
46	BDP hydrate (12 mg)	n=6,m=6	1.0
47	BDP hydrate (12 mg)	n=8,m=4	1.0
48	Salbutamol Sulphate (29 mg)	n=4,m=10	1.0
49	Salbutamol Sulphate (29 mg)	n=4,m=4	1.0
50	Salbutamol Sulphate (29 mg)	n=6,m=6	1.0
51	Salbutamol Sulphate (29 mg)	n=8,m=4	1.0

In the Examples 32 to 51, a range of drug/surfactant ratios (0.2% to 15%) was tested for each compound and each drug. The suspension stability was examined using a back light scattering technique. The suspension stability can be improved at surfactant concentration as low as 0.2% of drug weight. Drug deposition on the walls of the glass vials was also examined and reduced with increases in surfactant concentration. Drug/surfactant ratio as low as 0.1% was able to reduce drug deposition on the glass wall significantly, even at high water content in propellant, demonstrated in Examples 44 to 50.

Examples 52 to 67

Examples 52 to 67 were prepared as described for Examples 32 to 43 but using aluminium canisters rather than glass vials and 18.2g 1,1,1,2-tetrafluoroethane (P134a). In Examples 64 to 67 wet P134a containing 350ppm of water (prepared as described in Examples 44 to 51) was used.

Example	Drug (amount)	Surfactant type	Surfactant mg/inhaler
52	Salbutamol Sulphate (29 mg)	n=4,m=10	1.0
53	Salbutamol Sulphate (29 mg)	n=4,m=4	1.0
54	Salbutamol Sulphate (29 mg)	n=6,m=6	1.0
55	Salbutamol Sulphate (29 mg)	n=8,m=64	1.0
56	Salmeterol (8 mg)	n=4,m=10	1.0
57	Salmeterol (8 mg)	n=4,m=4	1.0
58	Salmeterol (8 mg)	n=6,m=6	1.0
59	Salmeterol (8 mg)	n=8,m=4	1.0
60	Fluticasone Propionate(6mg)	n=4,m=10	1.0
61	Fluticasone Propionate(6mg)	n=4,m=4	1.0
62	Fluticasone Propionate(6mg)	n=6,m=6	1.0
63	Fluticasone Propionate(6mg)	n=8,m=4	1.0
64	BDP hydrate (12 mg)	n=4,m=10	1.0
65	BDP hydrate (12 mg)	n=4,m=4	1.0
66	BDP hydrate (12 mg)	n=8,m=4	1.0
67	BDP hydrate (12 mg)	n=6,m=6	1.0

Examples 68 to 73

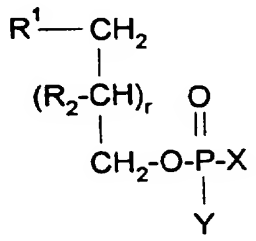
Examples 68 to 73 were prepared as described for Examples 21 to 31, the surfactant employed in each Example 68 to 73 being n=4, m=10.

Example 68	Surfactant (amount)	Propellant (amount)
Salmeterol xinafoate (14mg)	n=4, m=10 (3.9mg)	P134a (18.05mg)

	Surfactant (amount	Propellant (amount)
Example 69		
Amiloride HCl (32.3mg)	n=4, m=10 (1.7mg)	P134a (18.0mg)
Example 70		
Salmeterol xinafoate (9.9mg)	n=4, m=10 (2.2mg)	P227 (20.8mg)
Example 71		
Fluticasone propionate (26.7mg)	n=4, m=10 (3.0mg)	P227 (20.7mg)
Example 72		
Beclomethasone dipropionate (26.9mg)	n=4, m=10 (2.2mg)	P227 (20.7mg)
Example 73		
Amiloride HCl (30.7mg)	n=4, m=10 (2.0mg)	P227 (20.7mg)

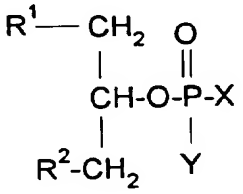
CLAIMS

1. A pharmaceutical aerosol formulation which comprises particulate medicament, a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant and a surfactant of general formula (Ia) or (Ib)



(Ia)

or



(Ib)

wherein:

R^1 represents:

$R_F(CH_2)_a$-$(CH{=}CH)_b$-$(CH_2)_c$-$(CH{=}CH)_d$-$(CH_2)_e$-A-;

R_F-$(CH_2)_f$-$OCH_2CH(CH_2OH)CH_2$-A-;

R_F-$(CH_2)_g$-$OCH_2CH(CH_2OH)$-A-;

wherein -A- represents -O-, -C(O)O-, $-R^6(R^7)N^+$-, (wherein each of R^6 and R^7 represents C_1-C_4 alkyl or hydroxyethyl), $-(CH_2)_t$-, wherein t=0 or 1 or $-C(O)N(R^9)$-$(CH_2)_q$-B, wherein q is an integer from 0 to 12, B represents -O- or -C(O)-, and R^9 is hydrogen or R^6,

and wherein the sum of a+c+e is from 0 to 17, the sum b+d is from 0 to 12 and each of f and g is from 1 to 12;

R_F-$(CH_2$-CH_2-$O)_h$-;

R_F-$(CH(CH_3)CH_2O)_h$-;

R_F-$(-CH_2$-CH_2-$S)_h$-,

wherein h is from 1 to 12; and

wherein R_F represents a fluorine-containing moiety having one of the following structures:

(a) $F(CF_2)_i$-, wherein i is from 1 to 18,

(b) $(CF_3)_2CF(CF_2)_j$-, wherein j is from 0 to 8,

(c) $R_F1(CF_2CF(CF_3))_k$-, wherein k is from 1 to 4, and R_F1 represents CF_3-, C_2F_5- or $(CF_3)_2CF$-,

(d) $R_F2(R_F3)CFO(CF_2CF_2)_l$ wherein l is from 1 to 6 and wherein each of R_F2 and R_F3 independently represents CF_3-, C_2F_5-, n-C_3F_7- or $CF_3CF_2CF(CF_3)$- or R_F2 and R_F3 taken together represent -$(CF_2)_4$- or -$(CF_2)_5$-, or

(e) one of the structures (a) to (d) in which one or more of the fluorine atoms are replaced by one or more hydrogen or bromine atoms and/or at least two chlorine atoms in a proportion such that at least 50% of the atoms bonded to the carbon skeleton of R_F are fluorine atoms, and wherein R_F contains at least 4 fluorine atoms,

r is 0 or 1;

R^2 represents R^1, hydrogen or a group OR,

wherein R represents a saturated or unsaturated C_1-C_{20} alkyl or C_3-C_{20} acyl;

and when r is 1, R^1 and R^2 may exchange their positions; and

each of X and Y independently represent:

hydroxyl;

$-OCH_2CH(OH)CH_2OH$;

$-O(CH_2CH_2O)_tR^3$,

wherein t is an integer from 1 to 5; and R^3 represents a hydrogen atom or C_1-C_4 alkyl group;

$-NR^4R^5$ or $N^+R^4R^5R^8$,

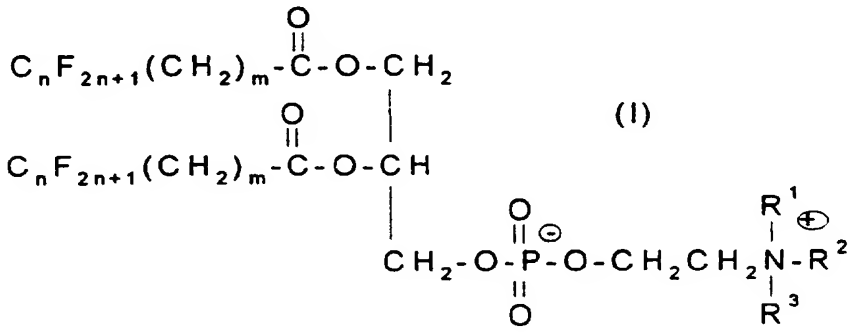
wherein each of R^4, R^5 and R^8 independently represents a hydrogen atom; a C_1-C_4 alkyl group, $-CH_2CH_2O(CH_2CH_2O)_sR^3$, wherein s represents an integer of from 1 to 5, or R^4 and R^5 when taken together

represent $-(CH_2)_q$ wherein q is an integer of from 2 to 5, or with the nitrogen atom R^4 and R^5 form a morpholino group;

$-O(CH_2)_pZ$ wherein Z represents a 2-aminoacetic acid group, $-NR^4R^5$ or $-N^+R^4R^5R^8$ where R^8 is as defined for R^4 and R^5 above, and p is an integer of from 1 to 5;

with the proviso that X and Y do not both represent hydroxyl or an ionized form derived from hydroxyl.

2. A pharmaceutical aerosol formulation which comprises particulate medicament, a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant and a surfactant of general formula (I)



(I)

wherein n is an integer of 1 to 18;
m is an integer of 0 to 17; and
R^1, R^2 and R^3 are each independently a hydrogen atom or a C_{1-4}alkyl group.

3. A formulation according to Claim 2, wherein R^1, R^2 and R^3 each represent methyl.

4. A formulation according to Claim 2 or 3, wherein n is an integer of 4 to 8.

5. A formulation according to Claim 4, wherein n is 4 or 6.

6. A formulation according to any of Claims 2 to 5, wherein m is an integer of 4 to 10.

7. A formulation according to Claim 6, wherein m is 4, 6 or 10.

8. A formulation according to any of Claims 1 to 7, wherein the surfactant is present in an amount of 0.05 to 15% w/w, relative to medicament.

9. A formulation according to Claim 8, wherein the surfactant is present in an amount of 0.5 to 10% w/w, relative to medicament.

10. A formulation according to any of Claims 1 to 9, wherein the particulate size of medicament is in the range of 1 - 10 microns.

11. A formulation according to any of Claims 1 to 10, wherein medicament is present in an amount of 0.01 - 1.0% w/w, relative to the total weight of the formulation.

12. A formulation according to any of Claims 1 to 11, wherein particulate medicament is selected from the group consisting of cromoglycate, salbutamol, salmeterol, terbutaline, reproterol, a beclomethasone ester, a fluticasone ester and (-)-4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl] amino]methyl]benzenemethanol.

13. A formulation according to Claim 12, wherein particulate medicament is selected from the group consisting of salmeterol xinafoate, salbutamol, fluticasone propionate, beclomethasone dipropionate and physiologically acceptable salts and solvates thereof.

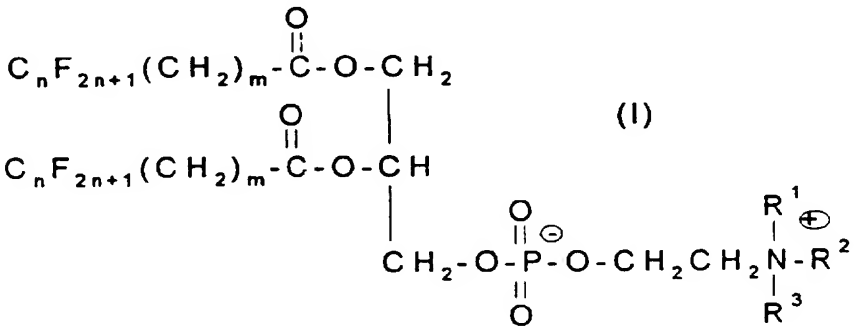
14. A formulation according to any of Claims 2 to 13, which comprises (a) an effective amount of a particulate bronchodilatory medicament, (b) an effective amount of a particulate antiinflammatory, (c) a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant, and (d) a surfactant of general formula (I).

15. A formulation according to any of Claims 1 to 14, wherein said propellant comprises a C_{1-4}hydrogen-containing fluorocarbon.

16. A formulation according to Claim 15, wherein said propellant is selected from 1,1,1,2- tetrafluoroethane(CF_3CH_2F) and 1,1,1,2,3,3,3-heptafluoro-n-propane (CF_3CHFCF_3).

17. A formulation according to any of Claims 2 to 16, which consists essentially of one or more particulate medicament, one or more fluorocarbon or hydrogen-containing chlorofluorocarbon propellant and a surfactant of formula (I).

18. A surfactant of general formula (I)



(I)

wherein n is an integer of 1 to 18;
m is an integer of 0 to 17; and
R^1, R^2 and R^3 are each independently a hydrogen atom or a C_{1-4}alkyl group;

with the proviso that m does not equal 4 when n equals 4.

19. A surfactant according to Claim 18, wherein R^1, R^2 and R^3 each represent methyl.

20. A surfactant according to Claim 18 or 19, wherein n is an integer of 4 to 8.

21. A surfactant according to Claim 20, wherein n is 4 or 6.

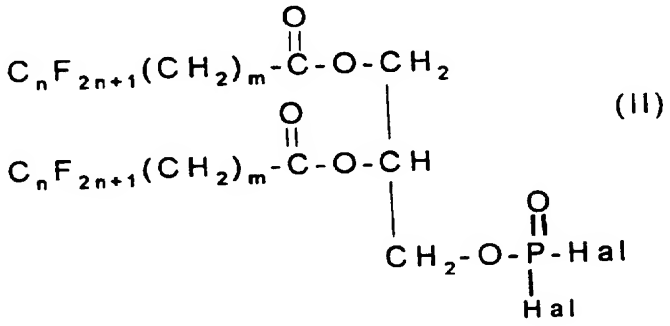
22. A surfactant according to any of Claims 18 to 21, wherein m is an integer of 4 to 10.

23. A surfactant according to Claim 22, wherein m is 4, 6 or 10.

24. A method of treating respiratory disorders, which comprises administration by inhalation of an effective amount of a formulation according to any of Claims 1 to 17.

25. A process of preparing a formulation according to any of Claims 1 to 17, which comprises dispersal of said medicament and surfactant in said propellant.

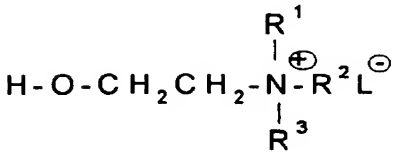
26. A process of preparing a surfactant according to any of Claims 18 to 23, which comprises reacting a compound of formula (II)



(II)

wherein Hal represents a halogen atom selected from fluorine, chlorine, bromine and iodine, with

(i) a compound of formula (III)



(III)

where L is a negatively charged counter ion, and

(ii) a hydroxylating agent.

27. A pharmaceutical aerosol formulation substantially as herein described.

28. A surfactant of formula (I) substantially as herein described.

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/IB 95/00866

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/72 C07F9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US,A,5 344 930 (RIESS ET AL.) 6 September 1994 see figures 1B,1C,5 see examples 10-13 & EP,A,0 478 686 cited in the application	18-23, 26,28 1-17,24, 25,27
Y	WO,A,86 04233 (RIKER LABORATORIES, INC.) 31 July 1986 see the whole document	1-17,24, 25,27
A	WO,A,92 00062 (MINNESOTA MINING AND MANUFACTURING COMPANY) 9 January 1992 cited in the application see the whole document	1-28

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
25 January 1996	07.02.96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Benz, K

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/IB 95/00866

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: ALthough claim 24 is directed to a method of treatment of the human/animal body the search has been carried out and baased on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 95/00866

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		JP-T-	5509085	16-12-93